Pyrimidones 1. Synthesis of some 1-Substituted-5-aryl- and (4,5-Diaryl)-2(1*H*)pyrimidones

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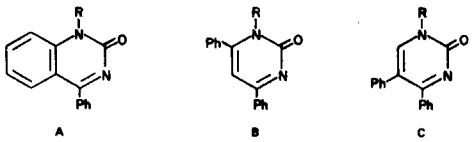
A series of 1-substituted-5-aryl-2(1*H*)pyrimidones has been prepared by a method involving condensation of an appropriate *N*-substituted urea with either 2-aryl-3-(dimethylamino)-acroleins or 2-arylmalondialdehydes. On biological investigation, several compounds exhibited some antiinflammatory activity.

J. Heterocyclic Chem., **16**, 545 (1979).

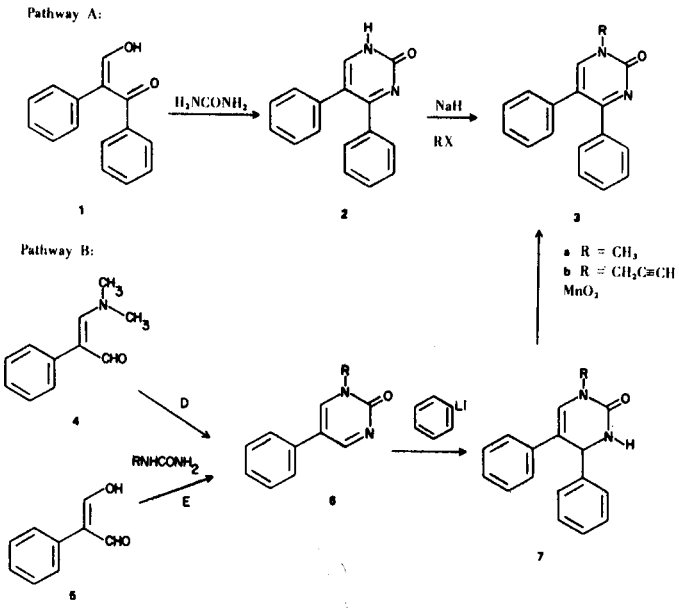
In a recent report (1) we have shown that 1-alkyl-4-phenyl-2(1*H*)quinazolinones exhibit pronounced anti-inflammatory activity. Compounds of this type (**A**) may be looked at as pyrimidinones fused with a phenyl ring at the 5,6 position. We were interested if the activity would be enhanced or retarded if the phenyl moiety were not rigidly bound to the pyrimidine ring but loosely attached as in **B** and **C**.



A B C

This rationale which was used in the 1,4-benzodiazepine series (2), resulted in subsequent loss of activity, but in this series compounds of type **C** did retain moderate antiinflammatory activity about which we will report separately.

Scheme 1

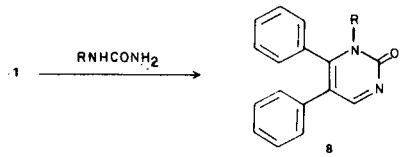


Compounds of type **B**, which will be reported in another paper, exhibited antiinflammatory activity, but were of greater interest as CNS agents.

The synthesis of the 4,5-diphenylpyrimidinones was accomplished by two separate routes as outlined in Scheme 1.

When urea was allowed to react with hydroxymethylenedeoxybenzoin, **2** was isolated in moderate yield (3). Alkylation of **2** was readily achieved with sodium hydride or sodium methoxide and the appropriate primary alkyl halide to furnish compounds of type **3** in good yields.

The alkylation of **2** in the 3 position and hence the formation of 1-alkyl-5,6-diphenylpyrimidinones (**8**) was ruled out based on the comparisons with previously published results on the reaction of **1** with *N*-methylurea (4), which led to the formation of **8** (R = CH_3), m.p. 251°. The product obtained by reaction of **2** wtih methyliodide melted at 133-136°.



The second route involves the condensation of 2-aryl-3-(dimethylamino)acroleins or 2-arylmalondialdehydes with an appropriate *N*-alkylurea to furnish the corresponding 1-substituted-5-aryl-2(1*H*)pyrimidinones (**6**) (Table 1). Surprisingly, these compounds also exhibited antiinflammatory activity and their biological profile will be discussed elsewhere. The 5-phenylpyrimidinones, in turn, were treated with a Grignard reagent or organolithium reagent to produce tetrahydropyrimidinones (*e.g.*, **7**) in good yield which were oxidized by manganese dioxide to yield the final products of type **3**. Products derived in this fashion were identical to those prepared *via* pathway A. This route is preferred over the first route because both aryl groups in the 4 and 5 position of the final

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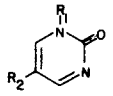
Table 1



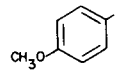
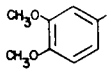
Compound No.	R_1	R_2	M.p., °C	Procedure Yield, %	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl
10	CH_3		186-189	D, 32 E, 84	dichloromethane/ether	$C_{11}H_{10}N_2O$				(6)
11	C_2H_5		166-169	D, 45	ethanol	$C_{12}H_{12}N_2O$	72.0 (72.0)	6.1 (6.3)	14.0 (14.4)	
12	*i*-propyl		120-122	D, 32	ether/pentane	$C_{13}H_{14}N_2O$	72.9 (72.8)	6.6 (6.3)	13.1 (13.2)	
13			172-174	E, 90	dichloromethane/ether	$C_{17}H_{14}N_2O_2$	73.4 (73.7)	5.1 (5.2)	10.1 (10.1)	
14	*i*-propyl		178-181	D, 41	dichloromethane/ether	$C_{13}H_{13}ClN_2O$	62.8 (62.5)	5.3 (5.2)	11.3 (11.1)	14.3 (14.5)
15	C_2H_5		196-199	D, 68	dichloromethane/ether	$C_{12}H_{10}Cl_2N_2O$	53.5 (53.6)	3.8 (3.8)	10.4 (10.4)	26.3 (26.5)
16	*i*-propyl		145-148	D, 30	methanol	$C_{14}H_{16}N_2O_2$	68.8 (69.2)	6.6 (6.4)	11.5 (11.1)	
17	CH_3		213-216	E, 76	ethanol	$C_{13}H_{14}N_2O_3$	63.4 (63.8)	5.7 (5.7)	11.4 (11.3)	

Table 1 (continued)

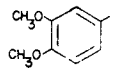
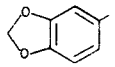
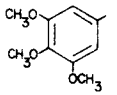
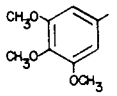
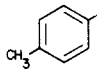
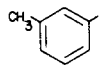
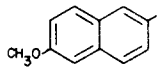
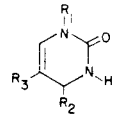
Compound No.	R_1	R_2	M.p., °C	Procedure Yield, %	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl
18	C_2H_5		171-173	D, 18 E, 76	dichloromethane/ether	$C_{14}H_{16}N_2O_3$	**64.6** **(64.8)**	**6.2** **(6.3)**	**10.8** **(11.0)**	
19	C_2H_5		159-160	E, 40	methanol	$C_{13}H_{12}N_2O_3$	63.9 (64.1)	5.0 (4.9)	11.5 (11.4)	
20	CH_3		193-196	E, 60	ethanol	$C_{14}H_{16}N_2O_4$	60.7 (60.6)	5.8 (6.1)	10.1 (10.4	
21	C_2H_5		169-172	D, 38 E, 82	dichloromethane/ether	$C_{15}H_{18}N_2O_4$	62.1 (61.8)	6.3 (6.0)	9.7 (9.5)	
22	C_2H_5		195-197	E, 80	dichlo-omethane/ether	$C_{13}H_{14}N_2O$	72.9 (72.6)	6.6 (6.6)	13.1 (13.1)	
23	*i*-propyl		110-113	D, 31	dichloromethane/ether	$C_{14}H_{16}N_2O$	73.7 (74.0)	7.1 (7.1)	12.3 (11.9)	
24	CH_3		258-259	E, 18	ethyl acetate	$C_{16}H_{14}N_2O_2$	72.2 (72.2)	5.3 (5.4)	10.5 (10.7)	

Table 2



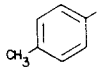
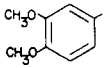
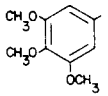
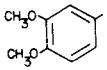
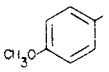
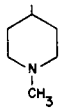
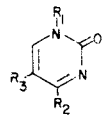
Compound No.	R_1	R_2	R_3	M.p., °C	Yield, %	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl
7a	CH_3			170-173	76	dichloromethane/ether	$C_{17}H_{16}N_2O$	77.3 (76.8)	6.1 (6.4)	10.6 (10.4)	
25	C_2H_5			157-160	80	dichloromethane/pentane	$C_{18}H_{18}N_2O$	77.7 (77.5)	6.5 (6.9)	10.1 (10.1)	
26	*i*-propyl			127-130	78	dichloromethane/pentane	$C_{19}H_{20}N_2O$	78.2 (78.1)	7.1 (7.2)	9.6 (9.4)	
27	C_2H_5			179-182	72	dichloromethane/ether	$C_{19}H_{20}N_2O$	78.1 (78.3)	6.9 (7.3)	9.6 (9.5)	
28	C_2H_5			156-158	27	dichloromethane/ether	$C_{19}H_{17}F_3N_2O$	65.9 (65.9)	5.0 (5.2)	8.1 (8.0)	
29	C_2H_5			134-137	75	dichloromethane/ether	$C_{18}H_{16}Cl_2N_2O$	**62.3 (62.0)**	**4.7 (4.8)**	**8.1 (8.3)**	20.4 (20.7)
30	C_2H_5			155-157	57	dichloromethane/ether	$C_{20}H_{22}N_2O_3$	71.0 (70.9)	6.6 (6.5)	8.3 (8.2)	
31	C_2H_5			160-163	64	dichloromethane/ether	$C_{21}H_{24}N_2O_4$	68.4 (68.3)	6.6 (6.5)	7.6 (7.6)	
32	C_2H_5			166-72	52	dichloromethane/ether	$C_{20}H_{21}ClN_2O_3$	64.4 (64.8)	5.7 (6.0)	7.5 (7.4)	9.5 (9.3)

Table 2 (continued)

Compound No.	R_1	R_2	R_3	M.p., °C	Yield, %	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl
33	*i*-propyl			134-138	65	dichloromethane/pentane	$C_{19}H_{19}ClN_2O$	69.8 (69.3)	5.9 (6.2)	8.6 (8.7)	(a)
34	*i*-propyl			115-120	71	dichloromethane/pentane	$C_{20}H_{22}N_2O_2$	74.5 (74.7)	6.9 (7.0)	8.7 (8.7)	
35	*i*-propyl			139-143	80	dichloromethane/pentane	$C_{20}H_{22}N_2O$	78.4 (78.2)	7.2 (7.3)	9.1 (8.9)	
36	*i*-propyl			174-176	75	dichloromethane/pentane	$C_{19}H_{19}ClN_2O$	69.8 (69.5)	5.9 (5.9)	8.6 (8.7)	
37	*i*-propyl			170-172	87	dichloromethane/ether	$C_{17}H_{18}N_2OS$	68.4 (67.8)	6.1 (6.3)	9.4 (9.4)	(a)
38	*i*-propyl			129-132	30	dichloromethane/pentane	$C_{19}H_{27}N_3O$	72.8 (72.5)	8.7 (8.7)	13.4 (13.5)	

(a) Reanalysis of the sample did not improve the values.

Table 3



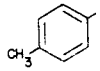
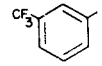
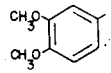
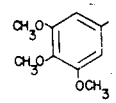
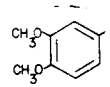
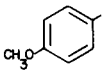
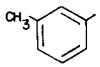
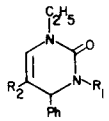
Compound No.	R_1	R_2	R_3	M.p., °C	Yield, %	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found C	H	N	Cl
3a	CH_3			133-136	78	dichloromethane/ether	$C_{17}H_{14}N_2O$	77.8 (77.6)	5.4 (5.7)	10.7 (10.8)	
39	C_2H_5			120-123	83	dichloromethane/pentane	$C_{18}H_{16}N_2O$	78.2 (78.2)	5.8 (6.0)	10.1 (10.1)	
40	*i*-propyl			138-140	75	dichloromethane/pentane	$C_{19}H_{18}N_2O$	78.6 (78.6)	6.3 (6.5)	9.7 (9.6)	
41	C_2H_5			198-201	77	dichloromethane/ether	$C_{19}H_{18}N_2O$	78.6 (78.7)	6.3 (6.1	9.7 (9.7)	
42	C_2H_5			174-176	50	dichloromethane/ether	$C_{19}H_{15}F_3N_2O$	66.3 (66.2)	4.4 (4.6)	8.1 (8.1)	
43	C_2H_5			198-201	76	dichloromethane/ether	$C_{18}H_{14}Cl_2N_2O$	62.6 (62.3)	4.1 (3.7)	8.1 (8.5)	20.5 (21.0) (a)
44	C_2H_5			172-175	77	dichloromethane/ether	$C_{20}H_{20}N_2O_3$	71.4 (71.1)	6.0 (6.1)	8.3 (8.4)	
45	C_2H_5			225-227	65	dichloromethane/ether	$C_{21}H_{22}N_2O_4$	68.8 (69.1)	6.1 (6.4)	7.6 (7.7)	
46	C_2H_5			189-192	50	methanol	$C_{20}H_{19}ClN_2O_3$	64.8 (65.1)	5.2 (5.3)	7.6 (7.6)	9.6 (10.0)

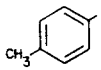
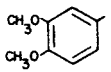
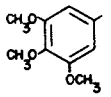
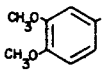
Table 3 (continued)

Compound No.	R_1	R_2	R_3	M.p., °C	Yield, %	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N	Cl
47	*i*-propyl			213-215	79	dichloromethane/pentane	$C_{19}H_{17}ClN_2O$	70.3 (70.1)	5.3 (5.3)	8.6 (9.0)	10.9 (11.2)
48	*i*-propyl			155-158	72	dichloromethane/ether	$C_{20}H_{20}N_2O_2$	75.0 (75.3)	6.3 (6.5)	8.7 (8.6)	
49	*i*-propyl			183-186	81	dichloromethane/ether	$C_{20}H_{20}N_2O$	78.9 (78.6)	6.6 (6.7)	9.2 (9.2)	
50	*i*-propyl			205-208	68	dichloromethane/ether	$C_{19}H_{17}ClN_2O$	70.3 (70.1)	5.3 (5.1)	8.6 (8.3)	10.9 (11.0)
51	*i*-propyl			163-166	78	dichloromethane/pentane	$C_{17}H_{16}N_2OS$	68.9 (68.6)	5.4 (5.6)	9.5 (9.5)	

(a) Reanalysis of the sample did not improve the values.

Table 4



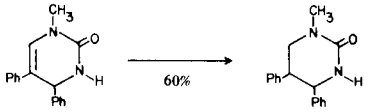
Compound No.	R_1	R_2	M.p., °C	Yield, %	Crystallization Solvent	Molecular Formula	Analysis Calcd. (Found) C	H	N
52	CH_3		148-150	77	ether/pentane	$C_{20}H_{22}N_2O$	78.4 (78.8)	7.3 (7.4)	9.1 (9.2)
53	CH_3		124-126	60	ether/pentane	$C_{21}H_{24}N_2O_3$	71.6 (71.4)	6.9 (7.0)	7.9 (7.8)
54	CH_3		123-125	80	ether/pentane	$C_{22}H_{26}N_2O_4$	69.1 (69.1)	6.9 (7.0)	7.3 (7.2)
55	$(CH_2)_2N(CH_3)_2$		118-120	66	ether	$C_{24}H_{31}N_3O_3$	70.4 (70.6)	7.6 (7.8)	10.3 (10.0)
56	$(CH_2)_2N(CH_3)_2 \cdot HCl$		185-188	90	dichloromethane/ether	$C_{22}H_{27}N_3O \cdot HCl$	68.5 (68.8)	7.3 (7.5)	10.9 (10.8)

product can be functionalized simply by varying the acrolein or dialdehyde and the Grignard reagent.

The Preparation of all 2-aryl-3-(dimethylamino)acroleins and 2-arylmalondialdehydes was accomplished by our previously described procedure (5). All 1-substituted-5-aryl-2(1*H*)pyrimidinones were obtained by two synthetic routes. Route **D** involves the condensation of 2-aryl-3-(dimethylamino)acroleins with *N*-substituted ureas in the presence of *p*-toluenesulfonic acid. Route **E** proceeds by a similar condensation with 2-arylmalondialdehydes. It was found that the use of the dialdehyde in place of the acrolein substantially increased the yield of the pyrimidinone.

The reaction can also be performed with *N*-substituted thioureas. Thus, when 2-phenyl-3-(dimethylamino)-acrolein was allowed to react with *N*-methylthiourea in the presence of *p*-toluenesulfonic acid, 1-methyl-5-phenyl-2(1*H*)pyrimidinethione was isolated in 28% yield.

Compound **7** is readily hydrogenated over platinum oxide at 3.5 atmospheres to yield the tetrahydropyrimidinone (**9**) in reasonable yield.



7 (R = CH_3) 9

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. Nuclear magnetic resonance spectra were determined on Varian A-60 and T-60 spectrophotometers using tetramethylsilane as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

Unless otherwise stated, all solutions of organic compounds were washed with brine and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

4,5-Diphenyl-2(1*H*)pyrimidinone (**2**).

A mixture of 2.0 g. of hydroxymethylene deoxybenzoin (**1**) and 2.0 g. of urea in 5.0 ml. of DMA was heated at 150-160° for one hour. After removal of the DMA under reduced pressure, the residue was dissolved in dichloromethane, washed well with water and dried over sodium sulfate. The solvent was removed under reduced pressure to furnish 1.6 g. of a yellow solid. This was triturated with ether to yield 800 mg. (37%) of **2**. A sample was recrystallized from dichloromethane/ether, m.p. 223-225°; ir (chloroform): 1645 cm^{-1}; nmr (deuteriochloroform): δ 12.0 (s, broad, 1), 8.3 (s, 1), 7.6-6.9 (m, 10).

Anal. Calcd. for $C_{16}H_{12}N_2O$: C, 77.4; H, 4.9; N, 11.3. Found: C, 77.6; H, 5.6; N, 11.1.

Repeated analysis did not improve the values.

4,5-Diphenyl-1-methyl-2(1*H*)pyrimidinone (**3a**).

To a solution of 0.5 g. of **2** in 20 ml. of THF and 5 ml. methanol, was added 120 mg. of sodium methoxide (after 5 minutes a precipitate formed). To this suspension was added 1.0 ml. of methyl iodide and the mixture was stirred for 15 minutes (a clear solution forms). The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane, washed with water and dried over sodium sulfate. Evaporation of the solvent furnished 600 mg. (78%) of **3a**. A sample was recrystallized from ethyl acetate/petroleum ether, m.p. 133-136°; ir (chloroform): 1660 cm^{-1}; nmr (deuteriochloroform): δ 7.75 (s, 1), 7.50-6.90 (m, 10), 3.65 (s, 3).

The material was identical in all respects to that obtained from the conversion of **7** to **3**.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.8; H, 5.4; N, 10.7. Found: C, 77.6; H, 5.7; N, 10.8.

4,5-Diphenyl-1-(2-propynyl)-2(1*H*)pyrimidinone (**3b**).

To a solution of 8.5 g. of **2** in 100 ml. DMA was added in portions 1.6 g. of sodium hydride (57%, in mineral oil, pentane washed). The mixture was stirred at room temperature for 30 minutes and then 5.0 ml. of propargyl bromide was added. The mixture was stirred at room temperature for 30 minutes and then was stored at 0° for 18 hours. The reaction mixture was concentrated to one half of the original volume and then was poured on 200 ml. cold water. The resulting precipitate was dissolved in chloroform and chromatographed on a column of silica gel using 1% methanol/chloroform to elute the product, which was crystallized from ethyl acetate/ether to yield 1.6 g. (16%) of **3b**, m.p. 152-156°; ir (chloroform): 3295, 1655 cm^{-1}; nmr (deuteriochloroform): δ 8.1 (s, 1), 7.6-7.0 (m, 10), 4.9 (d, 2), 2.65 (m, 1).

Anal. Calcd. for $C_{19}H_{14}N_2O$: C, 79.7; H, 4.9; N, 9.8. Found: C, 79.7; H, 5.2; N, 9.2.

Repeated analysis did not improve the values.

General Procedure D for the Preparation of 1-Alkyl-5-aryl-2(1*H*)-pyrimidinones (Table 1).

A mixture of equal weights of the corresponding 2-aryl-3-(dimethylamino)acrolein, *N*-alkylurea, and *p*-toluenesulfonic acid in toluene (or dioxane) was refluxed for 8 hours. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane, extracted twice with dilute sodium carbonate which was followed by an extraction with water. The organic phase was dried over sodium sulfate and the solvent evaporated to furnish the product which was then recrystallized from the solvent shown in Table 1.

General Procedure E for the Preparation of 1-Alkyl-5-aryl-2(1*H*)-pyrimidinones (Table 1).

A mixture of 0.2 mole of the corresponding 2-arylmalondialdehyde, 0.45 mole of the appropriate *N*-alkylurea, and 0.01 mole of *p*-toluene sulfonic acid in 200 ml. of toluene was refluxed for 30 minutes in an apparatus fitted with a Dean-Stark water separator. The reaction mixture was cooled and the resulting precipitate was filtered and then dissolved in dichloromethane. The organic phase was extracted with water, dried over sodium sulfate, and the solvent was evaporated under reduced pressure to furnish the product. This was recrystallized from the solvent listed in Table 1.

General Procedure for the Preparation of Compounds of Type **7** (Table 2).

To a suspension of 0.1 mole of the corresponding 1-alkyl-5-aryl-2(1*H*)pyrimidinone in 500 ml. THF, cooled in an ice bath, was added dropwise 0.11 mole of the corresponding aryl lithium compound (in THF) over a period of 30 minutes. The mixture was stirred at room temperature for 15 minutes and then poured on cold water. The resulting oil was extracted into chloroform, dried over sodium sulfate, and the solvent evaporated to furnish the product which was recrystallized from the solvent shown in Table 2.

General Procedure for the Preparation of Compounds of Type **3** by Manganese Dioxide Oxidation (Table **3**).

A mixture of equal weights of the compound of type **7** and manganese dioxide in benzene was refluxed for 18 hours. An additional equivalent weight of manganese dioxide was added and the mixture was refluxed for an additional 6 hours. The solids were filtered off and the residue was washed twice with benzene. The combined filtrates were evaporated under reduced pressure and the resulting residue was recrystallized from the solvent listed in Table 3.

General Procedure for the Alkylation of Compounds of Type **7** (Table 4).

To a solution of 0.01 mole of **7** in 150 ml. of DMA was added 0.01 mole of sodium hydride (57%, in mineral oil, pentane washed) in portions. The mixture was stirred at room temperature for 1 hour; then 0.01 mole of the appropriate alkyl halide was added. The mixture was stirred at room temperature for an additional 1 hour and was then poured into cold water, extracted into ethyl acetate and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished the product which was recrystallized from the solvent listed in Table 4.

4,5-Diphenyl-1-methyl-3,4,5,6-tetrahydro-2(1*H*)pyrimidinone (**9**).

A solution of 2.0 g. of **7** (R = CH_3) in 100 ml. of ethanol was hydrogenated in the presence of 0.2 g. of platinum oxide at 3.5 atmospheres until the theoretical uptake has been achieved. The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was crystallized from ethyl acetate/-ether to yield 1.2 g. (60%) of **9**, m.p. 218-222°; ir (chloroform): 3440, 1640 cm^{-1}; nmr (deuteriochloroform): δ 7.15 (m, 6), 6.75 (m, 4), 5.35 (m, 1), 4.75 (m, 1), 3.5 (m, 3), 3.05 (s, 3).

Anal. Calcd. for $C_{17}H_{18}N_2O$: C, 76.7; H, 6.8; N, 10.5. Found: C, 76.3; H, 7.1; N, 10.6.

Acknowledgement.

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(3) The tautomeric form in which **2** exists has not been firmly established. It may exist as the 5,6-diphenylpyrimidinone.

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